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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,509	05/18/2005	Alcaredo Koverech	725.1019	7229
20311 7590 03/18/2010 LUCAS & MERCANTI, LLP 475 PARK AVENUE SOUTH 15TH FLOOR NEW YORK, NY 10016				
EXAMINER BETTON, TIMOTHY E				
ART UNIT		PAPER NUMBER		
1627				
NOTIFICATION DATE		DELIVERY MODE		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

### Office Action Summary

**Application No.**

10/535,509

**Applicant(s)**

KOVERECH ET AL.

**Examiner**

TIMOTHY E. BETTON

**Art Unit**

1617

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 10-12 and 14-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 10-12 and 14-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB-08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Applicants' Remarks filed on 16 September 2009 has been acknowledged and duly made of record.

Essentially applicants' argue that their improvement of the prior art is that the administration of the claimed combination does not cause any increase in the blood level of testosterone. Applicants' further claim evidence of this disclosure in the 371/specification dated 18 May 2005 resulting in the recent amendment of claim 10.

Applicants' argument over claims 10-12 and 14-18 in the rejection under 35 U.S.C. § 103(a) as being obvious over Cavazza (US Patent No. 4,474,812, hereinafter ('812')), Cavazza (US Patent No. 6,245,378, hereinafter ('378)) and De Felice (US Patent No. 3,830,931, hereinafter ('931)) in view of De Simone (US Patent No. 6,037,373, hereinafter ('373)) and Xiu (US Patent No. 6,399,116, hereinafter ('116)) is considered but is not found persuasive.

In the instant specification on page 19 at Table 11, applicants' disclose:

**These results indicate that the activity of oral testosterone is exerted mainly through an increase in free and total blood testosterone, whereas the compound according to the invention acts in a different way, probably through restoration of" the physiological concentration of ROS.**

However, this disclosure above followed by Table 11 are not substantial evidence to moot the rejections of record. The disclosure above does not support or suggest a definite finding or result. Applicants' claim that this slight limitation holds some form of patentable weight in light of the history of prosecution of this present case is erroneous. The terminology is not definitive and does not adequately support or suggest that the references already made of record are improper.

The limitation of claim 10 drawn to the improvement comprising a lack of increase of blood testosterone levels is not confirmed or determined to be pharmaceutically related to the administration of carnitine or the lack thereof according to the content and scope of the disclosure on page 19 at Table 11.

Further, applicants' amendment conflicts with claim 11 which discloses a method of claim 10, in which andropause is caused by **aging**. However, on page 21 in the first paragraph of the same 371/specification, applicants' clearly state that these results confirm that it is the rise in free blood testosterone that causes the activity of testosterone in resolving the symptoms associated with **aging**.

Further, absent of any evidence clearly pointing out and delineating the distinctness in the references cited *supra* of the an effective amount of propionyl L-carnitine in combination with acetyl L-carnitine as opposed to those of the claimed invention, the rejection over claims 10-12 and 14-18 are hereby maintained.

Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

#### ***Status of the Claims***

Claims 1-9 are cancelled. Claims 10-12 and 14-18 are pending further prosecution on the merits.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10-12 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavazza (USPN 4,474,812) (hereinafter Cavazza ('812)) and Cavazza (USPN 6,245,378) (hereinafter Cavazza ('378)) and De Felice (USPN 3,830,931 in view of De Simone (USPN 6,037, 373) and Xiu (USPN 6,399,116 B1).

Cavazza ('812) teaches a novel therapeutic use of L-carnitine and a pharmaceutical L-carnitine-comprising composition [...], whose oral or parenteral administration to elderly

subjects brings about an improvement in the biochemical and behavioral parameters peculiar to senility (abstract only).

Cavazza ('812) teaches an embodiment drawn to L- carnitine which teaches the inventive objective of the claimed invention. Though Cavazza teaches embodiments drawn to treatment for senility in association with old-age, Cavazza teaches embodiments which to the skilled artisan would make instant claims 10-12 and 14-18 obvious.

Specifically, Cavazza teaches uses of L-carnitine [which] are already known. For instance, **L-carnitine has been used in the cardiovascular field in the treatment of acute and chronic myocardial ischaemia, angina pectoris, cardiac arrhythmias and insufficiency. In nephrology, L-carnitine has been administered to chronic uraemic patients who are subjected to regular haemodialysis treatment with a view to counteracting muscular asthenia and the onset of muscular cramps. Further therapeutic uses are the restoration of the HDL/LDL+VLDL ratio to normal and in total parenteral nutrition.**

Although the daily dose to be administered depends on the age, weight and general condition of the elderly subject [...] it has been found that, generally, from about 10 to about 30 mg of L-carnitine/kg of body weight/day or an equivalent amount of a pharmacologically acceptable salt thereof, is a suitable dose.

L-carnitine is compounded into the pharmaceutical compositions by using the usual excipients, diluents and adjuvant agents which are well-known in pharmaceutical technology for preparing orally and parenterally administrable compositions. An extensive list of such excipients and adjuvant agents as well as the methods for preparing solid and liquid oral unit

dosage forms such as tablets, capsules, solutions, syrups and the like and fluid injectable forms such as sterile solutions, is disclosed in the U.S. Pat. No. 3,830,931 to De Felice.

It has also been found that a pharmaceutical composition in unit dosage form which is particularly suited for the foregoing therapeutic uses comprises from about 500 to about 1,000 mg of L-carnitine.

Cavazza ('812) additionally teach the study of the effects of L-carnitine administration on some biochemical and behavioural parameters in old male rats.

Cavazza does not teach the use of propionyl- L-carnitine and acetyl L- carnitine.

Accordingly, Cavazza ('378) teaches a nutritional supplement for facilitating the adaptation of skeletal muscle in individuals undergoing programs of strenuous exercise and counteracting defatigation and weariness in asthenic individuals is disclosed, which comprises a combination of L-carnitine, acetyl L-carnitine and propionyl L-carnitine as basic active ingredients. Optional ingredients comprise isovaleryl L-carnitine, branched-chained aminoacids and creatine and/or phosphocreatine (abstract only).

Cavazza ('378) teaches an extensive embodiment of the indications for L-carnitine (column 2, lines 1-67).

Cavazza ('378) teaches mixtures, combinations and ratio strengths of acetyl and propionyl L-carnitine formulations which encompass the limitations of the instant claims (column 3, lines 64-67; column 4, lines 1-20).

**The skilled artisan would instantly recognize that many of the disorders and disease states are conditions common among geriatric patients.**

De Felice further confirms a well-established use of l-carnitine and carnitine derivatives among geriatric patients (please see Cases 1-12, columns 4-8).

The Cavazza references and De Felice do not specifically teach treatments for hormone disorders caused by andropause, such as the Markush members attributed to side effects and disorders *inter alia* listed in the instant claim 10.

However, De Simone does teach L-acetyl carnitine and L-propionyl carnitine for the treatment of diseases that are related to the ageing subject (e.g. arthritis, asthenia, osteoporosis, etc) (abstract only).

De Simone also teaches an embodiment directed to specific salts of the carnitine formulation (column 2, lines 8-16).

None of the references above directly teach a formulation indicated for the treatment for the decrease in testosterone and/or a decreased libido.

**However, Xiu does teach Rhodiola, preferably Rhodiola crenulata, to treat various conditions and diseases in mammals. Rhodiola crenulata is a Tibetan herb which has been discovered to have highly useful and beneficial properties heretofore unknown. Rhodiola crenulata is especially preferred to enhance blood oxygen levels, to enhance working capacity and endurance, to enhance memory and concentration, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to protect against oxidation, to modulate testosterone and estradiol levels, to modulate sleep, and to enhance sexuality, such as improve sexual performance.**

Xiu teaches a preferred embodiment drawn to the administration of carnitines in combination with Rhodiola crenulata (col 3, line 19). This adequately encompasses the



**inventive objective and subject matter limitation disclosed in instant claim 1. Particularly, instant claim 1 cites a method for the treatment of disorders caused by andropause comprising administering [...].**

**Specifically, Xiu teach andropause as a disorder indicated for treatment.**

Testosterone is considered to be a male virilizing hormone. Its effects include maintenance of muscle and bone mass, improving and/or enhancing sexual function and psychological well being among others. As males grow older, especially after the age of 35, a slow decline in testosterone levels is observed which is accompanied by symptoms that have been associated with the condition known as "andropause". Symptoms of andropause include lethargy, depression, lack of sexual desire and function, and loss of muscle mass and strength. (column 4, lines 55-67).

Thus, it would have been *prima facie* obvious to the skilled artisan at the time of invention to incorporate with or combine together the methods and teachings of Cavazza, De Felice, De Simone and Xiu as described above.

The Cavazza references teach methods and intended uses for L-carnitines and derivatives thereof. Cavazza ('812) and ('378) specifically teaches the study of the effects of L-carnitine administration on some biochemical and behavioral parameters in old male rats. The inventive objective in view of the claimed invention is drawn to elderly male subjects. De Felice and De Simone provide the primary motivation to combine via the administration of L-carnitine for an array of diseases associated with aging. Accordingly, Xui teaches embodiments of andropause being treated preferably by L-carnitines, L-carnitine mixtures, and compositions thereof.

The differences between the prior art of record and the claims at issue is directed to the newly amended claim 10, *which discloses the improvement comprising a lack of increase of blood testosterone levels*. All the references with the exception of Xui are silent with regard to the increase of blood testosterone levels and thus make the claimed invention obvious by virtue of teachings absent of this limitation. Further reasoning is due to the simple fact that carnitines and amino acids are not art-known or chemically constructed to increase blood testosterone levels. Thus by virtue of their chemical make-up, they are designed as hormone antagonists.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY E. BETTON whose telephone number is (571)272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627